## REMARKS

The rejection of claims 1-4 under 35 U.S.C. § 103(a) as being unpatentable over Sanchez-Ramos et al. (2000, Exp. Neurology, Vol. 164, pgs. 247-256), Inoue et al. (2001, Genes to Cells, Vol. 6, pgs. 977-986) and Elwood et al. (1998, Blood, Vol. 91, pgs. 3756-3765), is respectfully traversed.

### A. Critical Feature of the Present Invention

As described in "Background of the Invention" of the subject specification, several methods of inducing differentiation of Mesenchymal stem cells ("MSCs") into neuron like cells, e.g., by culturing MSCs in the presence of growth factors or hormones such as EGF or BDNF, have already been known (see page 1, lines 24-29 of the subject specification).

However, no one has conceived of or introduced the concept of expressing the basic helix-loop-helix (bHLH) transcription factors in the MSCs in order to transdifferentiate the MSCs into neuronal cells.

In this respect, as is claimed in claim 1, the critical feature of the present invention resides in the method for transdifferentiating the MSCs into neuronal cells by increasing the level of a basic helix-loop-helix (bHLH) transcription factor in the MSCs.

**B. Comparison of the Subject Invention with the Cited References**

As indicated by the Examiner in the outstanding Office Action, none of the cited references, i.e., Sanchez-Ramos et al., Inoue et al. and Elwood et al., teach the technical feature of the inventive method of transdifferentiating the MSCs with a bHLH transcription factor.

Specifically, Sanchez-Ramos et al. disclose that human and mouse bone marrow stem cells (BMSCs) can be induced to differentiate into neuronal cells by culturing BMSCc in the presence of EGF or BDNF, but does not teach using the bHLH transcription factor of the present invention to transdifferentiate MSCs. Sanchez-Ramos et al. also disclose that BMSCs when cultured in the presence of EGF or BDNF expressed the protein and mRNA for nestin, a marker of neuronal precursors (see Abstract of page 247). However, in view of a recent study, the identification of the protein and mRNA for nestin will not be sufficient and might be incorrect to confirm the differentiation into neuronal cells as discussed in paragraph C below.

Further, Inoue et al. merely disclose one of the bHLH genes, i.e., Math has a specific function in the nervous system to promote neuronal vs. glial fate determination. Accordingly, Inoue et al. is not a relevant teaching for the differentiation of MSCs into neuronal cells.

In addition, Elwood et al. is not concerned with the differentiation of MSCs into neuronal cells. The Abstract of Elwood et al. reads as follows:

> "The product of the SCL gene is a basic helix-loop-helix (bHLH) transcription factor that is essential for the development of hematopoietic stem cells in both the embryo and the adult. However, once the stem cell compartment is established, the function of SCL in subsequent differentiation and commitment events within normal hematopoietic cells remains undefined. The aim of the current study was to investigate this role using purified normal human hematopoietic $CD34^+$ cells."

Accordingly, Elwood et al. merely investigated the role of the SCL gene, one of the bHLH genes, and never conceived of transdifferentiation of MSCs into neuronal cells.

As discussed above, contrary to the Examiner's opinion that the ordinary artisan would have been motivated at the time of filing the subject application to transdifferentiate MSCs into neuronal cells by transducing a bHLH transcription factor in a viral vector in view of the combination of the three (3) cited references, no motivation exists to combine Sanchez-Ramos et al. with Inoue et al. and/or Elwood et al., since Inoue et al. and Elwood et al. are not relevant to the transdifferentiation of MSCs into neuronal cells and are instead merely concerned with one of the bHLH genes and the functions thereof and do not suggest the use of bHLH transcription factors for transdifferentiating MSCs into neuronal cells.

That is, although several kinds of bHLH genes were known in the art, the technical idea that bHLH transcription factors can be employed to transdifferentiate the MSCs into neuronal cells was not known at the time of filing the subject application and was the discovery of Applicant underlying the subject invention.

Since none of the cited references teach or suggest the key technical feature of the subject invention, i.e., the use of bHLH transcription factors for transdifferentiating the MSCs into neuronal cells, it cannot be obvious to those skilled in the art from the cited references taken alone or in combination without the aid of hindsight in view of the subject application.

**C. Recent Studies Supporting Inventiveness of the Subject Invention**

In view of recent studies, it has been found that the method of identifying the differentiation of BMSCs into neuron like cells employed in Sanchez-Ramos et al. is not sufficient or might be incorrect to confirm the differentiation of BMSCs into neuronal cells since nestin protein may be expressed in tissues other than in nervous system (see attached Exhibit 1, pp. 2897-2898 and attached Exhibit 2, page 2516 and Table 3, which are highlighted for emphasis) and may be also expressed in undifferentiated MSCs with no treatment (see also attached Exhibit 3, Abstract and Fig. 4).

Further, Lu et al. and Neuhuber et al. recently reported that genuine neuronal differentiation of MSCs would require not only the adoption of a neuronal

morphology and gene expression but also acquisition of electrophysiological properties of neurons (see attached Exhibit 4, page 189 and attached Exhibit 5, page 199).

Accordingly, it cannot be said that MSCs were differentiated into neuronal cells without demonstrating electrophysiological properties of differentiated MSCs. However, the subject invention demonstrated that MSCs expressing neurogenin (bHLH transcription factor) not only express neuron-specific proteins but also have electrophysiological properties (see working example 4, page 10 of the subject specification).

Meanwhile, in the developmental process, neuronal precursor cells or neuronal stem cells, which are able to be differentiated into neuron, are derived from ectoderm. However, mesenchymal stem cells (MSCs), which are able to be differentiated into bone cells or cartilage cells, etc, are derived from mesoderm. Therefore, the differentiation potential of MSCs is quite different from that of neuronal precursor cells or neuronal stem cells. Accordingly, it cannot be viewed obvious to transdifferentiate MSCs, which have an embryologically different differentiation potential compared with neuronal precursor cells or neuronal stem cells, into neuronal cells by expressing therein a certain bHLH transcription factor comprising neurogenin.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

## CONCLUSION

In view of the foregoing remarks, Applicant respectfully requests the reconsideration and reexamination of the present application and the timely allowance of the pending claims.

ATTACHED EXHIBITS

Exhibit 1: Phinney and Prockop, Stem Cells, 25:2896-2902, 2007

Exhibit 2: Wiese et al., Cellular and Molecular Life Sciences, 61:2510-2522, 2004

Exhibit 3: Tondreau et al., Differentiation, 72:319-326, 2004

Exhibit 4: Lu et al., J. Neurosci. Res., 77:174-191, 2004

Exhibit 5: Neuhuber et al., J. Neurosci. Res., 77:192-204, 2004

Respectfully submitted,

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## CERTIFICATE OF TRANSMISSION

I hereby certify that this Response w/attachments is being submitted to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 via EFS-Web on September 9, 2008.

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Audrey de Souza